

WHAT IS CLAIMED IS:

1. A high throughput screening system comprising:

a plurality of wells having a high transmittance portion through which cells present in said wells are optically observable in an area of observation;

5 two electrodes in each of said plurality of wells;

an optical detector configured to detect light emanating from said wells through said high transmittance portion;

10 a power supply connected to said electrodes; wherein said power supply and said electrodes are configured to apply a series of electric fields to cells within said area of observation, said electric fields having a spatial variation of less than about 25% of a mean field intensity within said area of observation, said electric fields being effective to controllably alter the transmembrane potential of a portion of said cells;

15 a data processing unit configured to interpret said light emanating from said wells through said high transmittance portion as ion channel activity resulting from said transmembrane potential alterations.

2. The high throughput screening system of Claim 1, wherein said plurality of wells are located in a multiwell plate.

20 3. The high throughput screening system of Claim 1, wherein said high transmittance portion is made from a material selected from the group consisting of glass, quartz, cycloolefin, Aclar, polypropylene, polyethylene and polystyrene.

4. The high throughput screening system of Claim 1, wherein said high transmittance portion exhibits less fluorescence when excited with UV light in the range of 250 nm to 400 nm than polystyrene.

25 5. The high throughput screening system of Claim 1, wherein said electrodes are located in a wall of said plurality of wells.

6. The high throughput screening system of Claim 5, wherein said electrodes are located in a bottom layer of said plurality of wells.

30 7. The high throughput screening system of Claim 2, wherein said multiwell plate comprises up to 96 wells.

8. The high throughput screening system of Claim 2, wherein said multiwell plate comprises greater than 96 wells.

9. The high throughput screening system of Claim 8, wherein said multiwell plate comprises greater than 384 wells.

5 10. The high throughput screening system of Claim 1, wherein said electrodes are made of a material selected from the group consisting of gold, platinum, palladium, chromium, molybdenum, iridium, tungsten, tantalum and titanium.

10 11. The high throughput screening system of Claim 2, wherein said multiwell plate comprises optically opaque materials or pigments to reduce the transmission of light.

12. The high throughput screening system of Claim 1, wherein said electrodes are separated by a gap within the range of about 1 to 4 mm.

13. The high throughput screening system of Claim 1, wherein said electrodes are separated by a gap within the range of about 0.1 to 1 mm.

15 14. The high throughput screening system of Claim 1, wherein said electrodes are separated by a gap within the range of about 0.01 to 0.1 mm.

16 15. The high throughput screening system of Claim 1, wherein said electrodes are charged to create an electrical field intensity of between 5 to 100 V/cm across said gap, and wherein the total charge transferred across the surface area of the electrically conductive material, in fluidic connection with the interior of the well is less than or equal to $100\mu\text{C}/\text{mm}^2$.

25 16. The high throughput screening system of Claim 1, wherein said plurality of wells further comprise an insulator orientated and configured so as to create an area of observation within said well in which the electrical field intensity varies by no more than 10 % from the mean electrical field intensity when said at least two strips of electrically conductive material are charged to create an electrical field intensity of between 5 to 100 V/cm across said gap, and wherein the total charge transferred across the surface area of the electrically conductive material, in fluidic connection with the interior of the well is less than or equal to $100\mu\text{C}/\text{mm}^2$.

30 17. The high throughput screening system of Claim 1, wherein said plurality of wells further comprise at least two satellite electrical conductors.

18. A high throughput screening system comprising:
sample wells;
liquid handling stations for adding reagents and/or cells to said sample wells; and

5 means for controlling the transmembrane potential of cells in said sample wells so as to selectively cause ion channel activity.

means for optically monitoring changes in said transmembrane potential.

19. The system of Claim 18, wherein said means comprises electrodes configured to create an electric field having a spatial variation of less than about 25% of
10 a mean field intensity within an area of observation.

20. The system of Claim 18, wherein said means for controlling the transmembrane potential comprise an electrode array assembly.

21. The system of Claim 20, wherein said electrode assembly array comprises 8 electrode assemblies.

15 22. The system of Claim 20, wherein said electrode assembly array comprises 96 electrode assemblies.

23. The system of Claim 20, wherein said electrode assembly array comprises greater than 96 electrode assemblies.

20 24. The system of Claim 20, wherein said system further comprises means for retractably moving said electrode assembly into and out of the wells of a multiwell plate.

25. The system of Claim 18, wherein said means for controlling the transmembrane potential comprises electrical conductors with two substantially parallel planar surfaces.

25 26. The system of Claim 25, wherein said electrical conductors are separated by a gap within the range of 1 to 4 mm.

27. The system of Claim 25, wherein said electrical conductors are separated by a gap within the range of 0.1 to 1 mm.

30 28. The system of Claim 25 wherein said electrical conductors further comprise a first insulator.

29. The system of Claim 28, wherein said first insulator comprises two planar surfaces orientated perpendicular to said substantially parallel planar surfaces of said electrical conductors and substantially parallel with respect to each other.

30. The system of Claim 28, wherein said electrical conductors further comprise a second insulator attached to said at least two electrical conductors, wherein said second insulator is interposed in said gap between said at least two electrical conductors to define the depth of said aqueous solution between said at least two electrical conductors.

31. The system of Claim 28, wherein said first insulator is composed of a low fluorescence material, wherein said low fluorescence material exhibits less fluorescence when excited with UV light in the range 250 nm to 400 nm than polystyrene of comparable size.

32. The system of Claim 30, wherein said second insulator is composed of a low fluorescence material, wherein said low fluorescence material exhibits less fluorescence when excited with UV light in the range 250 nm to 400 nm than polystyrene of comparable size.

33. The system of Claim 28, wherein said first insulator comprises an insulator selected from the group consisting of plastic, glass and ceramic.

34. The system of Claim 33, wherein said plastic is selected from the group consisting of nylon, polystyrene, Teflon (tetrafluoroethylene), polypropylene, polyethylene, polyvinyl chloride, and cycloolefin.

35. The system of Claim 25, wherein said electrical conductors comprise a conductor selected from the group consisting of gold, platinum, titanium, tungsten, molybdenum, iridium, vanadium, Nb, Ta, stainless steel and graphite.

36. The system of Claim 35, wherein said electrical conductors comprise a surface treatment to reduce electrolysis.

37. The system of Claim 36, wherein said surface treatment to reduce electrolysis comprises platinum black, gold black, iridium/iridium oxide, titanium/titanium nitride or polypyrrole films.

38. The system of Claim 19, wherein the electrical field intensity varies by no more than 10 % from the mean electrical field intensity when said at least two

electrical conductors are charged to create an electrical field intensity of between 5 to 100 V/cm across said gap, wherein the total charge transferred across the surface area of the electrical conductors in contact with said aqueous solution is less than or equal to 100 $\mu\text{C}/\text{mm}^2$.

5 39. The system of Claim 38, wherein the electrical field intensity varies by no more than 5% from the mean electrical field intensity when said at least two electrical conductors are charged to create an electrical field intensity of between 5 to 100 V/cm across said gap, wherein the total charge transferred across the surface area of the electrical conductors in contact with said aqueous solution is less than or equal to
10 100 $\mu\text{C}/\text{mm}^2$.

40. A method of screening a plurality of drug candidate compounds against a target ion channel comprising:

expressing said target ion channel in a population of host cells;
placing a plurality of said host cells into each of a plurality of sample
15 wells;
adding a candidate drug compound to at least one of said plurality of sample wells; and
modulating the transmembrane potential of host cells in said plurality of sample wells with a repetitive application of electric fields so as to set said
20 transmembrane potential to a level corresponding to a pre-selected voltage dependent state of said target ion channel.

41. The method of Claim 40, additionally comprising selecting a host cell line having a normal resting transmembrane potential corresponding to a second pre-selected voltage dependent state of said target ion channel.

25 42. The method of Claim 40, wherein said electric fields are biphasic.

43. The method of Claim 40, wherein electric fields cause an ion channel of interest to cycle between different voltage dependent states.

44. The method of Claim 40, wherein said electric fields cause an ion channel of interest to open.

30 45. The method of Claim 40, wherein said electric fields cause an ion channel of interest to be released from inactivation.

46. The method of Claim 40, wherein said one or more cells comprise a voltage sensor selected from the group consisting of a FRET based voltage sensor, an electrochromic transmembrane potential dye, a transmembrane potential redistribution dye, an ion sensitive fluorescent or luminescent molecule and a radioactive ion.

5 47. The method of Claim 40, wherein said target ion channel is selected from the group consisting of a potassium channel, a calcium channel, a chloride channel and a sodium channel.

10 ~~48.~~ The method of Claim 1, wherein said one or more electrical fields comprises stimulation with either a square wave-form, a sinusoidal wave-form or a saw tooth wave-form.

~~49.~~ The method of Claim 1, wherein said one or more electrical fields have an amplitude within the range of about 10 V/cm to about 100 V/cm.

~~50.~~ The method of Claim 15, wherein said one or more electrical fields have an amplitude within the range of about 20 V/cm to about 80 V/cm.

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